Cutaneous Reactive Hyperemia: Viscoelasticity Determines Response

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Two theories, myogenic and metabolic, have been proposed for reactive hyperemia. Since the metabolic theory implies that the changes in flow rate during reactive hyperemia must be explained in terms of changes in concentration of a vasodilator metabolite produced during anoxia, the rate of rise to peak reactive hyperemic flow should discriminate between these two possible mechanisms. Accordingly, changes in human cutaneous blood flow were monitored during postocclusive reactive hyperemia. The absolute values of both the rate of rise from zero blood flow to peak reactive hyperemic flow and the rate of recovery from peak reactive hyperemic flow to resting levels decrease with increasing durations of arterial occlusion. The time-dependent decrease in both rates is compatible with viscoelastic characteristics of the wall of resistance vessels and is not consistent with changes in concentration of a hypothesized vasodilator metabolite produced during occlusion. *J Invest Dermatol 89:197–200, 1987*

Reactive hyperemia is the temporary increase in blood flow to a tissue, organ, or extremity that occurs when the circulation to that tissue, organ, or extremity is released after a short period of vascular occlusion (Fig 1). The two widely held theories of the mechanism of reactive hyperemia are the metabolic theory and the myogenic theory [1]. Early in this century, Bayliss introduced the concept of a "myogenic" reaction, which consists of arteries and various other smooth muscle preparations reacting to stretching by contraction and to decreased tension by relaxation [2].

Reactive hyperemia could also be explained by the release of a vasodilator metabolite [3]. The accumulation and removal of such a vasodilator substance would be proportional to the amount of blood flow [4]. The rate of rise of erythrocyte flux, if proportional to the concentration of a putative vasodilator metabolite, should increase with longer durations of occlusion or else remain constant. The rate of recovery, if proportional to the concentration of a putative vasodilator metabolite, should correspond to the kinetics of the inactivation or clearance of the metabolite. In fact, the configuration of the individual reactive hyperemic response (Fig 1) shares the salient characteristics of an open one-compartment pharmacokinetic model with extravascular origin of the putative vasodilator metabolite [5–7]. Since the metabolic theory implies that the changes in flow rate during reactive hyperemia must be explained in terms of concentration of a vasodilator metabolite produced during occlusion, this author examined the kinetics and magnitude of the rise and recovery of erythrocyte flux during cutaneous reactive hyperemia to distinguish between the myogenic and metabolic theories (Fig 2).

Manuscript received October 20, 1986; accepted for publication February 9, 1987.

This work was supported by the Veterans Administration Merit Review Grant and the American Heart Association, Virginia Affiliate.

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Abbreviation:

ln: natural logarithm

Specifically, the most critical evidence is the characterization of the relationship between the rate of rise of erythrocyte flux and duration of arterial occlusion (Fig 3). If the rate of rise is directly related to duration of occlusion (Fig 3*a*), then the rate of rise could be directly related to the concentration of the putative vasodilator metabolite. The concentration of the putative vasodilator metabolite would be proportional to the duration of occlusion as implied by the metabolic theory.

If the rate of rise of erythrocyte flux remains constant despite changes in the duration of arterial occlusion (Fig 3*b*), then it may be that at all durations of occlusion tested the rate of vasodilation is maximal. With this view, even the lowest concentration of the putative vasodilator metabolite produced during the shortest duration of occlusion would provide the most rapid vascular smooth muscle relaxation produced by arterial occlusion.

If the rate of rise of erythrocyte flux is inversely related to duration of occlusion (Fig 3*c*), then the rate of rise could not be explained by the concentration of the putative vasodilator metabolite. This inverse relationship is incompatible with the determination of the configuration of the rise of erythrocyte flux to peak reactive hyperemic flow by a vasodilator metabolite.

MATERIALS AND METHODS

The forearm circulation was occluded in 10 healthy volunteers for 0.5, 1, 2, 4, and 6 min with a pneumatic cuff on the upper arm inflated 30–50 mmHg above brachial artery systolic pressure. Blood flow 4 cm distal to the antecubital crease was monitored continuously by laser Doppler velocimetry [8–10] (LD5000, MedPacific, Seattle, Washington) before, during, and after occlusion (Figs 1, 2).

The low-power (5-mW) helium-neon laser source emits light at 632.8 nm, which is delivered to the skin via flexible graded-index fiberoptic light guides. A portion of the incident light strikes nonmoving structures and is reflected with no shift in frequency. That portion which strikes moving blood cells is reflected with a shift in frequency (Doppler broadening). The reflected light is conducted from the tissue surface through a second fiberoptic light guide, mixed (heterodyned), and analyzed in real time by an analog processor that provides a continuous output of the

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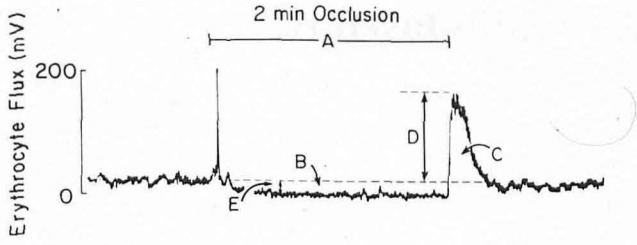

Figure 1. Laser Doppler velocimetric recording of postocclusive reactive hyperemia in the volar forearm skin after a 2-min brachial artery external occlusion. *A*, Duration of occlusion. *B*, Area under the time-occlusion curve ("debt"). *C*, Area under the time-reperfusion curve ("repayment"). *D*, Peak reactive hyperemic flow above baseline flow. *E*, Baseline (control) blood flow.

instantaneous mean Doppler frequency in the photocurrent identified by a square-law detector. The electrical analog of this output (mV) is displayed digitally and on a chart recorder. The signal is complex and composed of scattering from multiple classes of vessels. Although not a quantification of skin blood perfusion as volume/weight of tissue/unit time, laser Doppler velocimetry does produce outputs known to be related to fundamental skin perfusion characteristics, i.e., numbers of erythrocytes and their velocities [9–11]. The laser Doppler velocimeter probes are affixed by double-sided adhesive disks to the volar surface of the proximal forearm, 4 cm distal to the antecubital crease.

The electrical analog from the laser Doppler velocimeter was sampled at 5 Hz on an IBM personal computer (IBM-PC) using Lab Tech software. Since the initial deflection in simple overdamped oscillatory motion can be described as a decelerating parabolic function, the slope of rise was considered a parabolic function with the vertex at peak reactive hyperemic flow. The slope of the rise from immediately postocclusion to peak reactive hyperemic flow was calculated by least squares regression after a natural logarithmic transformation of peak flow erythrocyte flux (mV) minus the erythrocyte flux (mV) at t_n (time of the nth sample) vs time of peak erythrocyte flux (s) minus t_n (s). The slope of the recovery from peak reactive hyperemic flow to resting level was calculated by least squares regression of natural logarithm (ln) mV vs time (t) in seconds. All slopes of rise were positive and all slopes of recovery were negative. The absolute values are reported. Correlation coefficients calculated for individual slopes were all greater than 0.7.

All studies were conducted at an ambient temperature of 22.4 ± 1.0°C. The oral temperature of the subjects was 37.3 ± 0.4°C. All subjects were normotensive (<120/<80). All subjects were seated with the proximal forearm at heart level. The study began after resting for 30 min in the laboratory.

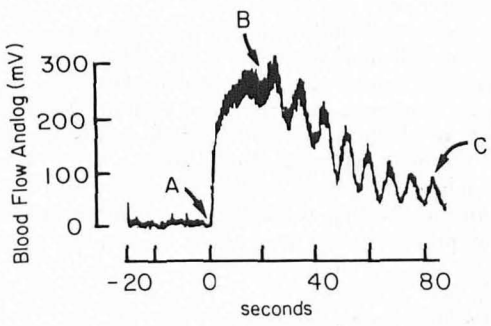

Figure 2. Recording of cutaneous reactive hyperemia in the volar forearm after 6-min occlusion. *Point A to point B* represents rise from zero blood flow at the end of occlusion to peak reactive hyperemic flow. *Point B to point C* represents recovery to resting level.

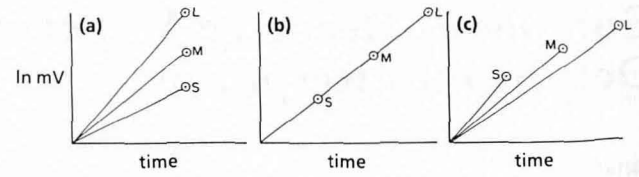

Figure 3. Three possible relationships between rate of rise of erythrocyte flux from zero flow to peak reactive hyperemic flow and duration of arterial occlusion: (*a*) the longer durations of occlusion are accompanied by more rapid rises in erythrocyte flux, (*b*) the rate of rise is constant, and (*c*) the shorter durations of occlusion are accompanied by more rapid rises in erythrocyte flux. *L*, *M*, and *S* refer to long, moderate, and short durations of occlusion, respectively. *Circles* represent peak reactive hyperemic flow, and the origin represents zero flow at the instant when the arterial occlusion is released.

RESULTS

Rates of Rise The mean slopes of rise to peak reactive hyperemic flow decreased with increasing duration of occlusion. The mean slopes of rise during the first 3 seconds decreased with increasing duration of occlusion. The mean slopes of rise during the first second only generally decreased with increasing duration of occlusion (Fig 4).

Rates of Recovery The absolute value of the mean slopes of recovery from peak reactive hyperemic flow to resting levels decreased with increasing duration of occlusion (Fig 4).

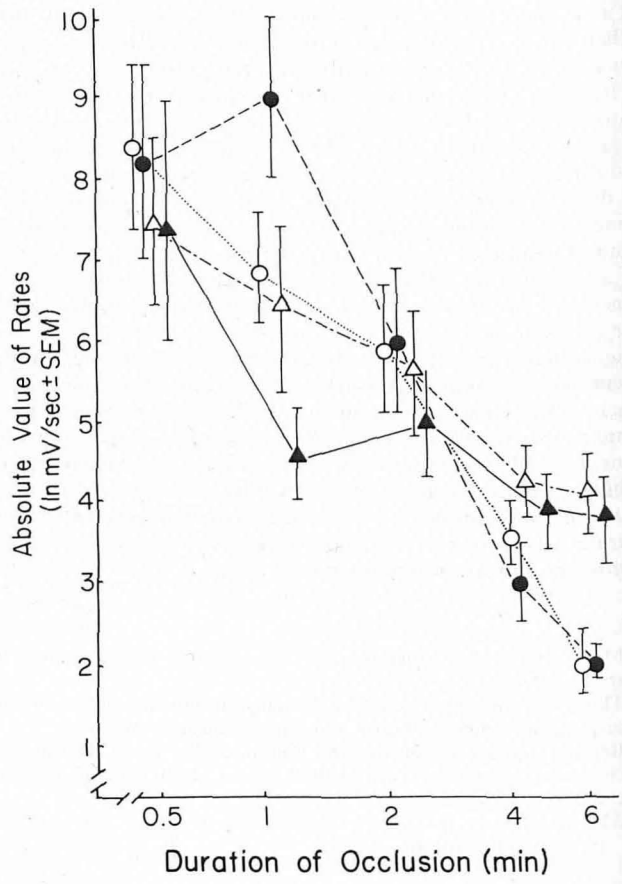

Figure 4. The absolute values of the mean slopes of rise from zero to peak reactive hyperemic flow (total, first 3 seconds, and first second only) and recovery from peak reactive hyperemic flow to resting levels decrease with increasing duration of occlusion. *Open triangles*, rise during first 3 seconds ($\times 10^{-1}$); *solid triangles*, rise during first second only ($\times 10^{-1}$); *open circles*, rise, total ($\times 10^{-1}$); *solid circles*, recovery ($\times 10^{-2}$).

Maximum Flow Peak reactive hyperemic flow (mV ± SEM) increased with increasing duration of occlusion: 47.7 ± 5.5, 90.6 ± 11.6, 129.1 ± 17.0, 147.2 ± 18.9, and 177.4 ± 22.2 for occlusions of 0.5, 1, 2, 4, and 6 min, respectively.

DISCUSSION

The time-dependent decrease in the absolute value of the rate constants for recovery of blood flow from peak reactive hyperemic flow to resting levels with increasing duration of occlusion does not distinguish between a myogenic mechanism and a metabolic mechanism. This finding does, however, impose a severe constraint on the metabolic theory, viz, that the simplest inactivation of a putative vasodilator metabolite would be described by second-order kinetics. This time dependency of recovery to resting blood flow levels has been previously observed in the heart [11] and in the hamster cheek pouch [12], and this observation is here extended also to cutaneous reactive hyperemia in humans.

Although the rate of rise to peak reactive hyperemic flow decreased with increasing durations of occlusion, the peak reactive hyperemic flow increases with increasing duration of occlusion. Thus, it is possible that these incremental increases in cutaneous blood flow represent the opening of less compliant microvessels that lower the overall average rate of rise. This is unlikely, since the rates of rise during the first 3 seconds and first second only also decrease with increasing duration of occlusion (Fig 4).

This time-dependent rate of increase in cutaneous blood flow from immediately post occlusion to peak reactive hyperemic flow does distinguish between myogenic and metabolic mechanisms. Since the metabolic theory implies that the changes in flow rate during reactive hyperemia must be explained in terms of changes in concentration of a vasodilator metabolite produced during occlusion, the metabolic theory can be rejected as the dominant mechanism in cutaneous reactive hyperemia. Clearly, the increased rate of rise at shorter durations of occlusion is unlikely due to a vasodilator metabolite, the concentration of which should increase with longer durations of occlusion. Alternatively, the time-dependent vasodilation from immediately post occlusion to peak reactive hyperemic flow is consistent with a second-order system based on the viscoelastic properties of the arteriolar wall. In other words, these data for both rates of rise and rates of recovery support a free overdamped oscillatory motion wherein the arteriolar viscous term dampens the movement of the vascular wall [13].

These results indicate that viscoelasticity determines the kinetics of blood flow in cutaneous reactive hyperemia. In this manner, and consistent with the Johnson-Wayland model, viscoelasticity produces the requisite feedback lag in which the myogenic mechanism determines the configuration of the reactive hyperemic response [14]. Notwithstanding the apparent dominance of a myogenic mechanism, a role for metabolic factors cannot be completely excluded.

Importantly, viscoelasticity in resting mammalian smooth muscle can be related to crossbridge attachment. Both resistance to stretch and stress relaxation, attributed to a viscoelastic property of the muscle, are markedly affected by the presence or absence of calcium in the bathing medium. The calcium-dependent resistance to stretch in resting mammalian smooth muscle implies that crossbridges are attached and thus able to resist stretch in noncontracting smooth muscles. When the muscle is stretched, the breaking and subsequent re-formation of links in nonstrained positions account for most of the apparent viscoelasticity [15,16]. Further, the effect of selected vasodilators in enhancing the relaxation rate is likely due to Ca^{++} sequestration or extrusion [17,18]. The tethering action of the gel-like tissue structures surrounding the vessels may also contribute to the distensibility [19].

Folkow has pointed out that the Bayliss mechanism may have a major role in reactive hyperemia by affecting the precapillary vessels rather than the entire resistance section. Thus, the myogenically active smooth muscles of these small vessels, which provide resistance to flow and determine the capillary surface area open to flow, act like continuously active stretch receptors with inherent contractility [20]. Johnson has proposed a modification of this model in which wall tension, and not the length of the vascular smooth muscle cell, is the controlled variable [14]. Folkow's model of the myogenic mechanism is based on both the cylindrical geometry of the arteriole and a passively distensible sensor component connected with a contractile element. The Johnson-Wayland modification holds that these components are connected in series and not in parallel, i.e., an excitable membrane, the sensor unit, is connected in series with the contractile apparatus. Further, the contractile apparatus consists of both viscous and elastic elements, implying viscoelastic behavior in the myogenic mechanism [14].

Autoregulation is the ability of tissues or organs to keep their blood flow essentially constant during changes in the arterial perfusion pressure head. This mechanism has also been explained by the myogenic and metabolic theories [21]. Both the autoregulatory response and the reactive hyperemic response appear to be of intrinsic vascular nature [21]. A role for the myogenic response in autoregulation has been argued by Bevan on the presence of the myogenic response, the size of which depends on the amount of stretch and which occurs with wall stresses of the order encountered in vivo [22].

The terms myogenic and metabolic are more descriptive than mechanistic. Myogenic tone specifies tone that is independent of external chemical stimulation and that is stretch-dependent [22]. The metabolic theory is based on the accumulation of a vasodilator substance formed or released in response to hypoxia or depletion of a critical substrate due to reduced tissue perfusion. Since metabolic events inside the vascular smooth muscle cells may have a role in myogenic tone, the term metabolic becomes ambiguous with the strict reliance on conceptual evolutionary baggage from earlier times in vascular physiology. Folkow alluded to this in his discussion of the myogenic theory, pointing out that the increased contractility with stretch must ultimately be ascribed to an event(s) of the contractile process, including membrane excitability, excitation-contraction coupling, energy metabolism, and chemomechanical transduction [20].

Finally, since tissues and organs vary widely in their metabolic activity and blood flow, their mechanisms of reactive hyperemia may differ. Thus, the wide range of blood flow through the skin is important in thermoregulation, and cutaneous blood flow is usually greatly in excess of the metabolic needs of the skin [23]. As most tissues, e.g., the heart, do not have such an enormous perfusion reserve, metabolic factors may be more important. Thus, the results of this study are specific for cutaneous reactive hyperemia and cannot be extrapolated to other organs or tissues.

The author thanks N. Thompson and A. Yun for technical assistance, L. Marcade and C. Frye for preparation of the manuscript, and M. Thames, M.D., for his critical review of the manuscript and helpful suggestions.

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